REMARKS

Claims 1-17 are pending in the application. Claims 1, 3, 5, 12, 14, 15, 17 are currently amended. Claims 2, 4, and 13 are cancelled without prejudice or disclaimer. Accordingly, claims 1, 3, 5-12, 14-17 will be pending in the application upon entry of the amendments presented herein.

Claims 1, 3, 5, 12, 14, 15, 17 have been amended to claim more fully the recited subject matter and to make minor editorial changes. Support for the amendment to Claims 1 and 12 may be found in the specification as filed at least, for example, at page 20, line 8 to page 21, line 9 and page 36, line 23 to page 37, line 9, page 7, lines 10 to 17 and Claims 2, 4, and 13 as originally filed. Claims 3, 5, 14, 15, 17 were amended to correct dependencies resulting from the cancellation of claims 2, 4, and 13. No new matter has been added.

Amendment and cancellation of the claims herein are not to be construed as acquiescence to any objections/rejections set forth in the instant Office Action and/or any previous Office Action were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in this or one or more subsequent patent applications.

Specification

Objection is made to the abstract of the disclosure as originally filed. In particular, the Office Action at page 2 indicates that "the abstract does not disclose that which is new in the art to which the invention pertains" and that because "the patent application is in the nature of an improvement to old processes or compositions, the abstract should include the technical disclosure of the improvement". Applicants respectfully disagree.

However, without acquiescing in any way to the objection and in order to expedite prosecution, Applicants have amended the abstract of the disclosure as set forth above. Applicants respectfully submit that the abstract fully complies with the requirements of 37 C.F.R. §1.72(b), and MPEP 608.01(b) .

Claim Rejections – 35 U.S.C. §112

Claims 1-11 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants have cancelled claims 2 and 4 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims. Regarding claims 1, 3, and 5-11, Applicants respectfully disagree and traverse the rejection.

The Examiner states that in step of (2) of claim 1, "the water-sparingly-soluble/hardly extractable protein that is denatured previously" lacks antecedent basis or is indefinite. However, claim 1 has been amended to add steps (2) and (3) which respectively provide "an immunogen for raising an antibody against the water-sparingly-soluble/hardly extractable protein..." and "the antibody against the water-sparingly-soluble/hardly extractable protein..." Step (4) of claim 1 (previously step (2) of claim 1) has been amended to recite "adding the antibody of step (3) to the protein solution of step (1) or a dilution of the protein solution of step (1) to form a reaction mixture wherein the reaction mixture contains more than 0.03% (W/V) of the ionic surfactant contained in the aqueous solvent of step (1)." With regard to "the ionic surfactant used in step (1)", Applicants have clearly defined it as "the same ionic surfactant as that contained in the aqueous solvent of step (1)." The above amendment further clarifies this matter and obviates the rejection.

The Examiner also states that the term "denatured" is indefinite because the specification dose not appear to define one or more standards for ascertaining "denatured." Based on the disclosure of the specification (*e.g.*, at least in Example 5 describing the Denaturation of Proteins), it would be clear to a person skilled in the art that the "water-sparingly-soluble/hardly extractable" protein is "denatured." For example, the Examiner also understands the term "denatured" in citing that Knowles and Marchesi describe a protein that is denatured.

The Examiner additionally states that, in step (2) of claim 1, "the ionic surfactant used in step (1)" lacks antecedent basis or is indefinite. Step (4) of claim 1 (previously step (2) of claim 1), as amended, recites "the ionic surfactant contained in the aqueous solvent of step (1)." The above amendment provides antecedent basis for "the ionic surfactant" recited in step (4) and, thus, obviates the rejection.

The Examiner further states that in step (2)(b) of claim 1, "the ionic surfactant" lacks antecedent basis. Step (4) of claim 1 (previously step (2) of claim 1) has been amended to recite "adding the antibody of step (3) to the protein solution of step (1) or a dilution of the protein solution of step (1) to form a reaction mixture wherein the reaction mixture contains more than 0.03% (W/V) of the ionic surfactant contained in the aqueous solvent of step (1)." Thus, step (4) of claim 1 (previously step (2) of claim 1), has been amended to specify that the concentration of the ionic surfactant in the reaction mixture is more than 0.03% (W/V). The above amendment clarifies this matter and obviates the rejection.

The Examiner states that in claim 17, "the antibody according to any one of claims 12" is not clear. However, claim 17, as amended, recites "the antibody of claim 12." The above amendment clarifies this matter and obviates the rejection.

Applicants respectfully submit that claim 1, and claims 3, 5-11 depending therefrom, and claim 17 fully comply with the requirements of 35 U.S.C. §112, second paragraph and, therefore, respectfully request reconsideration and withdrawal of the rejections.

Claim Rejections – 35 U.S.C. §102

Claims 1, 4-7 and 11-17 are rejected under 35 U.S.C. §102(b) as anticipated in view of U.S. Patent 4,658,022 to Knowles and Marchesi ("Knowles and Marchesi"). Applicants have cancelled claims 4 and 13 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims. Regarding claims 1, 5-7, 11-12, and 14-17, Applicants respectfully disagree and traverse the rejection.

In order to anticipate the invention as claimed, the cited referenced must teach each and every element of the claim. The presently claimed invention, as currently amended, includes the detection of an antigen-antibody complex in an aqueous solution containing an ionic surfactant selected from the group consisting of sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride and a mixture thereof at a concentration higher than 0.03% (W/V). Thus, the present invention includes using an antibody in an aqueous solution containing an extractable

protein and an ionic surfactant, as recited in the claims, at a concentration higher than 0.03% (W/V), where the antibody is raised against the extractable protein denatured with the same ionic surfactant at a concentration of higher than 0.3% (W/V).

In contrast, Knowles and Marchesi fail to teach or suggest using an ionic surfactant at a concentration higher than 0.03% (W/W) in a solution for detecting the extractable protein or higher than 0.3% (W/V) in a solution for preparing the immunogen for raising the antibody against the extractable protein. Instead Knowles and Marchesi teach the use of a chaotrope (*i.e.*, guandine) for extracting and denaturing the extractable protein [col. 8, line 42 - col. 9, line 2]. In particular, Knowles and Marchesi do not specifically teach or suggest that the formation of the antigen-antibody complex can be carried out in the presence of more than 0.03% (W/V) of an ionic surfactant selected from sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride or a mixture thereof.

Knowles and Marchesi teach that "the sample-chaotrope mixture **will normally be diluted** as a separate step..." (emphasis added) [col 8, lines 63-64], and "[f]or guanidine, this preferably requires dilution fo a concentration less than about 1.0 molar, with about 0.3 molar being particularly preferred [col 8, line 67-col 9, line 2]. In contrast, the concentration of the ionic surfactant in the Applicants' method does not need to be diluted for detection using an antibody. As stated at the second paragraph at page 7 of the specification as filed:

> It was found that even if the concentration of the ionic surfactant in the aqueous solvent in the [protein extraction step] is for example higher than 0.3% (W/V), formation of an antigen-antibody complex in the sample (protein) solution extracted with said aqueous solvent is not inhibited. **That is, the antigen-antibody complex in the [antibody addition step] can be formed in the presence of the ionic surfactant at a concentration of higher than 0.3% (W/V), preferably 1% (W/V) or more.** Even if the sample solution should be diluted for the purpose of quantitative analysis etc., it is not necessary that the ionic surfactant is diluted to a concentration of 0.03% (W/V) or less believed in the prior art to be necessary for excellent antigen-antibody reaction, and this means that the method of the present invention can be practiced without sacrificing the high extraction power of the ionic surfactant. [emphasis added]

Knowles and Marchesi neither teaches nor suggests the concentrations of any ionic surfactant that can be used nor do they provide one with any guidance how to adapt their method using chaotropes for use with ionic surfactants, as being claimed by the Applicants. Thus, the teachings of Knowles and Marchesi do not put one of skill in the art in possession of the presently claimed invention. In contrast, Applicants have clearly taught how to make and how to use ionic surfactants at a concentration higher than 0.03% (W/V) and 0.3% (W/V) in immunoassays.

Because Knowles and Marchesi do not teach or suggest the use of an ionic surfactant, selected from sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride and a mixture thereof, at a concentration higher than 0.3% (W/V) or even 0.03% (W/V), the patent does not anticipate the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of 1, 5-7, 11-12, and 14-17, under 35 U.S.C. §102(b).

Claims 1, 4-7 and 9 are rejected under 35 U.S.C. §102(b) as anticipated in view of U.S. Patent 4,427,782 to Caldwell and Schacter ("Caldwell and Schacter"). Applicants have cancelled claim 4 without prejudice or disclaimer, thereby rendering the rejection moot as to that claim. Regarding claims 1, 5-7, and 9, Applicants respectfully disagree and traverse the rejection.

As indicated above, in order to anticipate the invention as claimed, the cited referenced must teach each and every element of the claim. The presently claimed invention, as currently amended, includes preparing an immunogen in the presence of an ionic surfactant selected from the group consisting of sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride and a mixture thereof at a concentration higher than 0.03% (W/V), and forming an antigen-antibody complex in the presence of the same ionic surfactant at a concentration higher than 0.03% (W/V).

In contrast, Caldwell and Schacter teach preparing an immunogen in a solution of 0.1% SDS [col. 4, lines 44-51]. However, Caldwell and Schacter neither teach nor suggest preparing an immunogen in a solution with a concentration of SDS higher than

0.3% (W/V). Caldwell and Schacter teach extracting the major outer membrane protein with SDS [col. 7, lines 53-56] and detecting the extracted protein by adding antibody [col. 7, lines 57-60], but neither teach nor suggest detecting an antigen-antibody complex in a solution with a concentration of SDS higher than 0.03% (W/V). Rather, Caldwell and Schacter are silent regarding the final concentration of the ionic surfactant in the mixture.

Because Caldwell and Schacter do not teach or suggest extracting a protein in a solution having a concentration of SDS higher than 0.3% (W/V) nor forming an antigen-antibody complex in a solution having a concentration of SDS higher than 0.03% (W/V), the patent does not anticipate the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 5-7, and 9, under 35 U.S.C. §102(b).

Claim Rejections – 35 U.S.C. §103

Claims 2, 3, and 8-10 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Knowles and Marchesi in view of Powell, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Unit 17.14A, John Wiley & sons, Inc. (1995) ("Powell"). Applicants have cancelled claim 2 without prejudice or disclaimer, thereby rendering the rejection moot as to that claim. Regarding claims 3 and 8-10, Applicants respectfully disagree and traverse the rejection.

In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention.

As acknowledged by the Examiner on page 8 of the Office Action, Knowles and Marchesi do not teach "particular sodium dodecyl sulfate (SDS) concentrations and 2-mercaptoethanol concentration in the 'aqueous solvent'" or "a boiling step." The Examiner has further cited Powell as an alleged remedy for this deficiency of Knowles and Marchesi.

However, Claim 1 as currently amended includes preparing an antibody from an immunogen extracted using an aqueous solvent containing an ionic surfactant from the group consisting of sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride, and a mixture thereof at a concentration higher than 0.3% (W/V) and detecting the antigen-antibody comples in the presence of higher than 0.03% of the same ionic surfactant. Similarly, Claims 3 and 8-10, which depend from Claim 1, also contain the limitations of Claim 1 (37 C.F.R. §1.75(c)).

As indicated in the above response to the rejection under 35 U.S.C. §102(b), Knowles and Marchesi do not teach or suggest using a solution having a concentration of any of the recited ionic surfactants higher than 0.03% (W/V) for detecting an antigen-antibody complex or for raising an antibody. Likewise, Powell also does not teach or suggest either detecting an antigen-antibody complex using a solution having a concentration of ionic surfactant higher than 0.03% (W/V) or raising an antibody using a solution having a concentration of ionic surfactant higher than 0.3% (W/V). At most, Powell teaches the use of 20% (W/V) SDS for analysis of glycopeptides (*e.g.*, by SDS-PAGE, reverse-phase liquid chromatography, gel-filtration chromatography; paragraph spanning pages 17.14.5-6), but not for detecting antigen-antibody complexes, as in the methods of the invention. Therefore, Powell does not make up for the deficiencies in Knowles and Marchesi, nor would one be motivated to combine Powell with Knowles and Marchesi to arrive at the invention being claimed.

Thus, there is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the references in the manner proffered by the Examiner. Assuming for the sake of argument that there were such motivation, the combination does not teach or suggest each and every element of the claimed invention because neither reference teaches or suggests detecting an antigen-antibody complex using a solution having a concentration of ionic surfactant higher than 0.03% (W/V) or raising an antibody using a solution having a concentration of ionic surfactant higher than 0.3% (W/V). Therefore, because the cited combination of references does not put one of ordinary skill in the art in possession of the claimed invention, one of ordinary skill in the

art would not have a reasonable expectation of success in making and using the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection of claims, 1, 3,and 8-10, under 35 U.S.C. §103(a).

Claim 1 is rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent 4,658,022 to Youngner and Knoll ("Youngner and Knoll") in view of Salk, A Simplified Procedure for Titrating Hemagglutinating Capacity of Influenza-Virus and the Corresponding Antibody. J Immunol 1944 49: 87-98 ("Salk"). Applicants specifically disagree and traverse the rejection.

In the present case, the references cited by the Examiner fail to provide the requisite motivation to combine; fail to provide a reasonable expectation of success; and fail to teach or suggest all of the claim limitations.

Claim 1, as amended, includes preparing an immunogen using an aqueous solution having a concentration of an ionic surfactant higher than 0.3% (W/V), and detecting an antigen-antibody complex in a solution containing higher than 0.3% (W/V) of the same ionic surfactant. Specifically, the ionic surfactants include sodium dodecyl sulfate, lithium dodecyl sulfate, sodium lauryl sarcosine, hexadecyltrimethyl ammonium bromide, hexadecyltrimethyl ammonium chloride, hexadecyl pyridinium chloride, or a mixture thereof. Similarly, Claims 3, 5-11, which depend from Claim 1, also contain the limitations of Claim 1 (37 C.F.R. §1.75(c)).

Neither of these two references cited by the Examiner teaches or suggests using a solution with an ionic surfactant either higher than 0.3% (W/V) or 0.03% (W/V). Specifically, Youngner and Noll describe using a lipid to solubilize proteins [col. 4, lines 33-75], but not do not teach or suggest using an ionic surfactant to solubilize proteins. Neither does Salk teach or suggest using an ionic surfactant to solubilize proteins or detecting antigen-antibody complexes in a solution containing an ionic surfactant. As acknowledged by the Examiner on page 10 of the Office Action, Youngner and Noll do not teach "a hemagglutination inhibition test step of adding the antibodies raised in step (2) to the soluble extracted protein of step (1)." The Examiner has cited Salk and has presented it as an alleged remedy for this deficiency of Youngner and Noll.

However, the Claim 1 as currently amended recites "an aqueous solvent containing an ionic surfactant." The deficiency of Youngner and Noll regarding the use

of ionic surfactants still remains, and Salk does not make up for this deficiency regarding the use of ionic surfactants. Thus, Younger and Noll and Salk uniformly fail to teach or suggest using an ionic surfactant and, therefore, do not teach or suggest each and every element of the claimed invention.

In the absence of such a teaching or suggestion present in the cited references or in the general knowledge in the field, the skilled artisan could not arrive at the claimed invention. In view of this deficiency, the skilled artisan would lack the requisite motivation to combine the references and would further lack a reasonable expectation of success. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 1, and claims 3, 5-11 depending therefrom, under 35 U.S.C. §103(a).

Additionally, Applicants cite evidence of unexpected results in support of the nonobviousness of the invention. The antibody raised against the extractable protein dissolved in the aqueous solvent containing higher than 0.3% (W/V) ionic surfactant is highly sensitive and resistant to the concentrations of the ionic surfactant used in the methods of the invention. None of the cited references discloses such an antibody with these features.

As described in the originally filed specification, the use of the antibody of the present invention that is raised against the denatured protein as above is highly preferable as compared to the antibody raised against the native protein, as shown in Figures 4 and 14 of the specification as filed. Specifically, in Figure 4, ovalbumin (64 ng/ml) is dissolved in an aqueous solvent at various concentrations of SDS and the formation of the antigen-antibody complex (absorbance) is measured where the antibody has been raised against the native ovalbumin (see also "Example 2", page 30 to 31 of the specification as filed). From Figure 4, it is clear that the formation of the antigen-antibody complex is affected by as little as 0.041% of SDS (see also Table 2) and almost completely inhibited by 0.123% of the ionic surfactant.

In sharp contrast, Figure 14 shows that the formation of the antigen-antibody complex can be detected with high sensitivity, *i.e.*, as little as several nanograms of the protein per milliliter, even in the presence of SDS at a concentration of 1% (W/V) when the antibody of the invention is used (page 40, lines 18 to 27 of the specification as filed). These results would not be expected from the teachings of any of the cited

references, nor do the cited references describe the production of an antibody that can be used to detect antigen-antibody complexes in the presence of higher than 0.3% (W/V).

Thus the methods of the invention are not obvious, at least because the teachings of the cited references either alone or in combination would not put one possession of a sensitive antibody resistant to ionic surfactants that could be used to detect antigen-antibody complexes in an aqueous solvent comprising an ionic surfactant recited in the claims at a concentration higher than 0.3% (W/V). Therefore Applicants respectfully request withdrawal of the rejections of claim 1, and claims 3, and 8-10 under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the applications with claims 1, 3, 5-12, 14-17 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

Applicants believe that no other fees are required for consideration and entry of this paper. Nevertheless, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **04-1105**, under Order No. 61625(70232).

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Respectfully submitted,

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